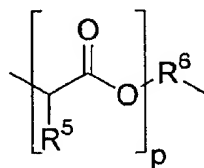


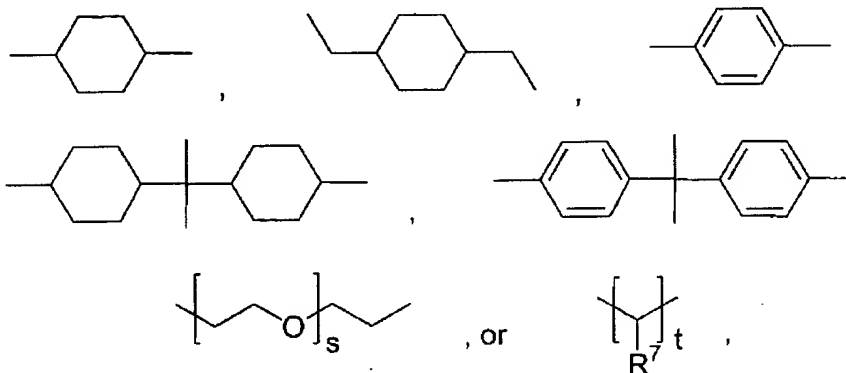
Application No. 09/854,435

Page 7

R<sup>1</sup> is:

where:

p is an integer of 1 to 20;

R<sup>5</sup> is hydrogen or C<sub>1-4</sub> alkyl; andR<sup>6</sup> is:

where:

s is an integer of 0 to 30;

t is an integer of 2 to 200; and

R<sup>7</sup> is hydrogen or C<sub>1-4</sub> alkyl;R<sup>11</sup> is hydrogen or C<sub>1-6</sub> alkyl and R<sup>12</sup> is C<sub>1-6</sub> alkyl; or R<sup>11</sup> and R<sup>12</sup> together are C<sub>3-10</sub> alkylene; and

at least 0.1 mole percent of the total polyol content is a diol of the formula HO-R<sup>4</sup>-OH, where R<sup>4</sup> is the residue of a diol containing at least one functional group independently selected from the group consisting of amide, imide, urea, and urethane groups.

## REMARKS

Entry of this amendment is respectfully requested. No new matter is added by the amendment, because the amended application is fully supported by the application as filed.

Claims 1 - 15 and 17 - 35 are in this application, claims 15 and 16 having been cancelled, claims 1, 5 - 8, 12 - 14, 17, and 18 having been amended, and no claims having been added by this amendment.

Application No. 09/854,435

Page 8

**The amendment:**

- (1) corrects typographical errors in the specification at page 13, lines 9 - 12 and 14 - 19 (the errors and corrections being obvious when compared to the remainder of the specification),
- (2) deletes the paragraph at page 14, lines 14 - 29 (which is a substantial duplicate of the paragraph at page 17, line 25 - page 18, line 11),
- (3) alters the Markush language in claims 1, 17, and 18 to respond to the 35 USC 112, ¶2 rejection (no change being intended by the amendment); and
- (4) amends claims 5 - 8 and 12 - 14 by replacing "-O-R<sup>x</sup>-" with "R<sup>x</sup>", where x is 1 or 2, as appropriate (the errors and corrections being obvious when compared to the remainder of the specification and claims).

**The restriction requirement**

The Examiner has required restriction between claims 1 - 19, "to a polyorthoester and method of making", and claims 20 - 35, "to a device for orthopedic restoration and bioerodible implants". Applicants note that claims 20 and 21 are indeed drawn to a device for orthopedic restoration and a bioerodible implant, and further note that claims 22 - 35 are drawn to pharmaceutical compositions and methods of treatment. Applicants confirm the oral election of claims 1 - 19, without traverse, but respectfully request that claims 20 and 21 be examined with claims 1 - 19, since claims 20 and 21 require the presence of no additional element (such as the active ingredient of the pharmaceutical composition of claim 22) but merely specify a particular device comprising the polyorthoester of claim 1, so that such claims should be patentable if claim 1 is found patentable.

**The 35 USC 112, ¶2 rejection**

Claims 1, 17, and 18 were rejected under 35 USC 112, ¶2, for indefiniteness for "improper Markush group practice". Applicants respectfully submit that present PTO practice allows the use of language other than "selected from the group consisting of" (see MPEP 2173.05(h), subpart I); however, in the interest of avoiding unnecessary dispute and because no change in substance is required or intended by change in wording, Applicants have amended these claims to the "selected from the group consisting of" language. Withdrawal of the rejection is requested in view of the amendment.

**The 35 USC 103(a) rejection**

Claims 1 - 19 were rejected under 35 USC 103(a) as unpatentable over Heller et al., US Patent No. 5,968,543 in view of Sparer et al., US Patent No. 4,549,010. This rejection is respectfully traversed.

**The invention**

The invention, as claimed in claim 1 and its dependent claims, is a polyorthoester that is the reaction product of a diketene diacetal and at least two diols: a diol that is a hydroxy-terminated ester of an  $\alpha$ -hydroxy acid, and a diol that contains at least one amide, imide, urea, or urethane functional group. The polyorthoester may also contain one or more of a "hard" diol and a "soft" diol, as described in the specification and defined in the claims.

Heller et al.

Applicants agree with the Examiner's characterization of Heller et al. as showing polymers with controlled physical state and bioerodibility, made from a diketene acetal and incorporating esters of

Application No. 09/854,435

Page 9

$\alpha$ -hydroxy acids and diols generally as claimed, except that Heller et al. do not disclose the use in their polymers (polyorthoesters) of diols containing functional groups selected from amide, imide, urea, and urethane groups.

Sparer et al.

Applicants agree with the Examiner's characterization of Sparer et al. as showing bioerodible poly(ortho ester) thermoplastic polymers from diketene diacetals and a mixture of diols that may contain functionalities capable of engaging in hydrogen bonding, such as amide, imide, urea, and urethane groups, though Applicants note that Sparer et al. requires not only the hydrogen-bonding diols but also long-chain non-polar flexible diols containing 4 to 22 carbon atoms and does not admit of the presence of other diols (other than "highly rigid, symmetrical diols" — a term of which no substantial further definition and no exemplification is given, and up to 1% triols or higher polyols).

#### Discussion

The Examiner reasons that "It is the Examiner's position that the use of [diols containing functional groups selected from amide, imide, urea, and urethane groups — *omitted from text of rejection but understood to be intended*] as indicated would have been obvious in view of the secondary reference to Sparer et al. . . . Thus, the preparation of polyorthoesters incorporating structural units as claimed would have been *prima facie* obvious based on a combination of references as explained supra." Applicants respectfully disagree.

It is settled law that to establish a *prima facie* case of obviousness in a combination rejection, the Examiner must show that (1) there is some suggestion or motivation in the references themselves or in the knowledge of the art to combine the references, (2) that there would be a reasonable expectation of success if the references were so combined, and (3) that the combination of references must teach or suggest all the claim limitations. The suggestion to make the combination and the expectation of success must both be found in the references and not from Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), cited in MPEP 2142. The mere fact that references *can* be modified or combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990), also cited in MPEP 2142. Also, a statement that modifications of the prior art to meet the claimed invention would have been "*well within the ordinary skill of the art* at the time the invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993), also cited in MPEP 2142.

The Examiner's assertion that "the use of diols containing functional groups selected from amide, imide, urea, and urethane groups as indicated [in the polyorthoesters of Heller et al.] would have been obvious in view of the secondary reference to Sparer et al. . . . Thus, the preparation of polyorthoesters incorporating structural units as claimed would have been *prima facie* obvious" fails to meet that required standard.

Applicants respectfully submit that there is no suggestion or motivation in the references themselves or in the knowledge of the art to combine the references. Accepting that the references teach as the Examiner has described them, the Examiner admits that there is no teaching in Heller et al. of the use in polyorthoesters of diols containing functional groups selected from amide, imide, urea, and urethane groups, and it is evident that there is no teaching in Sparer et al. of the use in polyorthoesters

Application No. 09/854,435

Page 10

of diols that are hydroxy-terminated esters of  $\alpha$ -hydroxy acids; nor is there anything in either reference to suggest the proposed combination.

Also, if the combination were to be made, there is no guidance as to what features of each reference should be retained and what discarded. Applicants concede that both references speak of polyorthoesters based on diketene diacetals such as 3,9-di(ethylidene)-2,4,8,10-tetraoxa-spiro[5.5]undecane (DETOSU) and related diketene diacetals; but emphasize that Heller et al. does not require the long-chain non-polar flexible diols (or the highly rigid, symmetrical diols) required by Sparer et al., while Sparer et al. does not permit of the  $\alpha$ -hydroxy acid-containing diols or optional "soft" diols of Heller et al. Thus the only guidance as to the combination is in the present application, which may not be used to guide the combination.

Finally, nothing in either reference suggests the desirability of the proposed combination. That suggestion may only be found in the disclosure of the present application, which may not be used to guide the combination, so that the first prong of the test is failed.

Further, since there is no motivation for the combination, there can be no expectation of the success of such a combination if made, so that the second prong of the test is also failed.

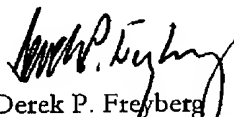
Applicants therefore submit that Claims 1 - 19 are not unpatentable over Heller et al. in view of Sparer et al., and withdrawal of the rejection is requested

#### Conclusion

Attached hereto is a marked up copy of the changes made to the application by the current amendment. The attached pages are captioned "Amendments to show changes made".

Entry of the amendment, reconsideration of the restriction requirement as to claims 20 and 21, and re-examination and allowance of claims 1 - 21, are respectfully requested.

Respectfully submitted,



Derek P. Freyberg  
Attorney for Applicants  
Reg. No. 29,250

Customer No. 25213  
Heller Ehrman White & McAuliffe LLP  
275 Middlefield Road  
Menlo Park, CA 94025-3506  
(650) 324-7014  
December 27, 2002

SV 408933 v1  
12/27/02 3:10 PM (10008.1191)

Amendments to show changes made  
(Additions in bold, deletions in strikethrough)

**Specification, paragraph at page 13, lines 9 - 12:**

With respect to the individual "α-hydroxy acid containing" unit, p is preferably 1 to 6, more preferably 1 to 4, most preferably 1 or 2; R<sup>5</sup> R<sup>4</sup> is preferably hydrogen or methyl; and in the above definitions of R<sup>6</sup> R<sup>5</sup>, s is preferably 2 to 12, more preferably 2 to 6 and most preferably 2; and t is preferably 4 to 12, more preferably 4 to 6 and most preferably 6.

**Specification, paragraph at page 13, lines 14 - 19:**

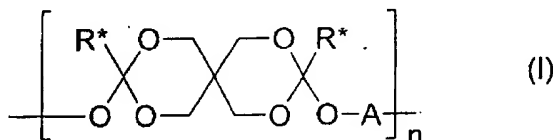
With respect to the individual "soft" unit, q is preferably 1 to 6 and more preferably 1 to 3; and in the definitions of R<sup>3</sup>, x is preferably 2 to 12, more preferably 2 to 6 and most preferably 2; y is preferably 4 to 12, more preferably 4 to 6 and most preferably 6; R<sup>8</sup> is preferably hydrogen; R<sup>9</sup> and R<sup>10</sup> R<sup>6</sup> and R<sup>7</sup> are preferably identical, more preferably an unbranched C<sub>4</sub>-C<sub>12</sub> alkylene and most preferably an unbranched C<sub>6</sub>-C<sub>12</sub> alkylene; R<sup>8</sup> is preferably hydrogen; R<sup>9</sup> is preferably methyl; R<sup>11</sup> R<sup>10</sup> is preferably hydrogen and R<sup>12</sup> R<sup>11</sup> is preferably methyl.

**Specification, paragraph at page 17, lines 18 - 24:**

The polyorthoesters may also be prepared by reaction of the diketene acetal with the chosen diol(s) under similar reaction conditions, but in the presence of a "chain stopper" (a reagent that terminates polyorthoester chain formation). Suitable chain stoppers are C<sub>5-20</sub> alkanols, especially C<sub>10-20</sub> alkanols. The chain stopper is preferably present in from 1 - 20 mol% based on the diketene acetal.<sup>7</sup> The polyorthoesters thus prepared have lower molecular weights with a lower molecular weight dispersion than those prepared by the reaction of the diketene acetals with only diols.

**Claims 1, 5 - 8, 12 - 14, 17, and 18:**

1. (Amended) A polyorthoester of formula I:

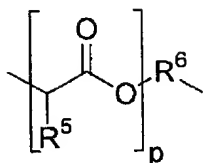


where:

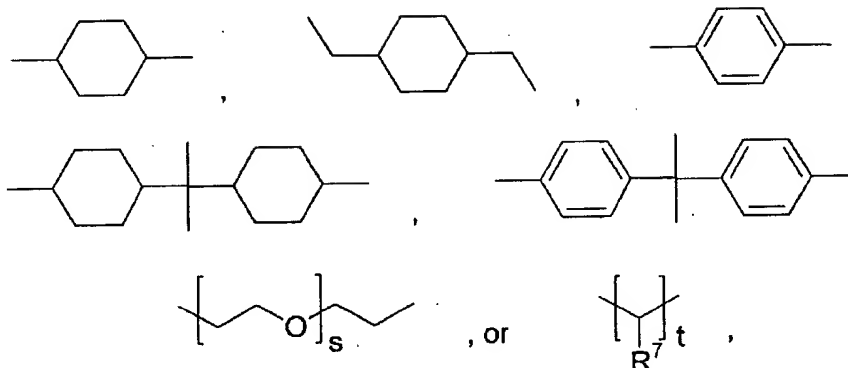
R\* is a C<sub>1-4</sub> alkyl;

Application No. 09/854,435

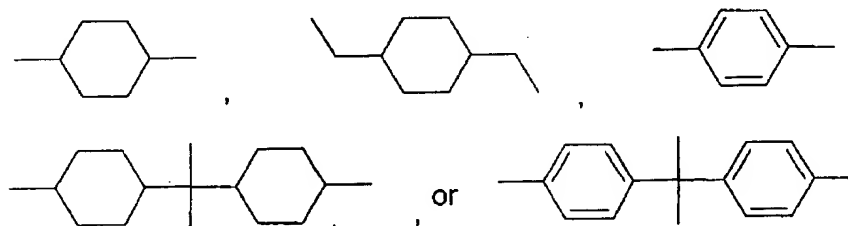
Page 12

 $n$  is an integer of at least 5; and $A$  is  $R^1$ ,  $R^2$ ,  $R^3$ , or  $R^4$ , where $R^1$  is:

where:

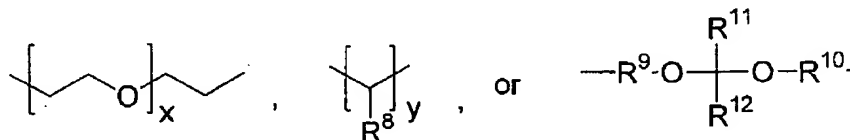
 $p$  is an integer of 1 to 20; $R^5$  is hydrogen or  $C_{1-4}$  alkyl; and $R^6$  is:

where:

 $s$  is an integer of 0 to 30; $t$  is an integer of 2 to 200; and $R^7$  is hydrogen or  $C_{1-4}$  alkyl; $R^2$  is:

Application No. 09/854,435

Page 13

R<sup>3</sup> is:

where:

x is an integer of 0 to 30;

y is an integer of 2 to 200;

R<sup>8</sup> is hydrogen or C<sub>1-4</sub> alkyl;R<sup>9</sup> and R<sup>10</sup> are independently C<sub>1-12</sub> alkylene;R<sup>11</sup> is hydrogen or C<sub>1-6</sub> alkyl and R<sup>12</sup> is C<sub>1-6</sub> alkyl; or R<sup>11</sup> and R<sup>12</sup> together are C<sub>3-10</sub> alkylene; andR<sup>4</sup> is a diol containing at least one functional group independently selected from the group consisting of amide, imide, urea, and urethane groups;in which at least 0.1 mol% of the A units are R<sup>1</sup>, and at least 0.1 mol% of the A units are R<sup>4</sup>.

5. (Amended) The polyorthoester of Claim 1 which comprises about 1 to about 50 mole percent of units in which A is R<sup>1</sup> - O - R<sup>1</sup>.

6. (Amended) The polyorthoester of Claim 5 which comprises about 2 to about 30 mole percent of units in which A is R<sup>1</sup> - O - R<sup>1</sup>.

7. (Amended) The polyorthoester of Claim 6 which comprises about 5 to about 30 mole percent of units in which A is R<sup>1</sup> - O - R<sup>1</sup>.

8. (Amended) The polyorthoester of Claim 7 which comprises about 10 to about 30 mole percent of units in which A is R<sup>1</sup> - O - R<sup>1</sup>.

12. (Amended) The polyorthoester of Claim 1 where R<sup>3</sup> R<sup>4</sup> is hydrogen or methyl.

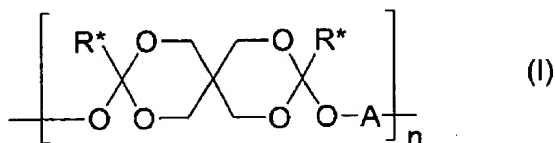
13. (Amended) The polyorthoester of Claim 1 which comprises up to about 20 mole percent of units in which A is R<sup>2</sup> - O - R<sup>2</sup>.

14. (Amended) The polyorthoester of Claim 1 which comprises about 60 to about 99.9 mole percent of units in which A is R<sup>2</sup> - O - R<sup>2</sup>.

Application No. 09/854,435

Page 14

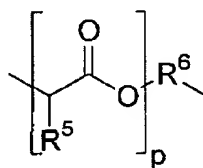
17. (Amended) A process of preparing a polyorthoester of formula I:



where:

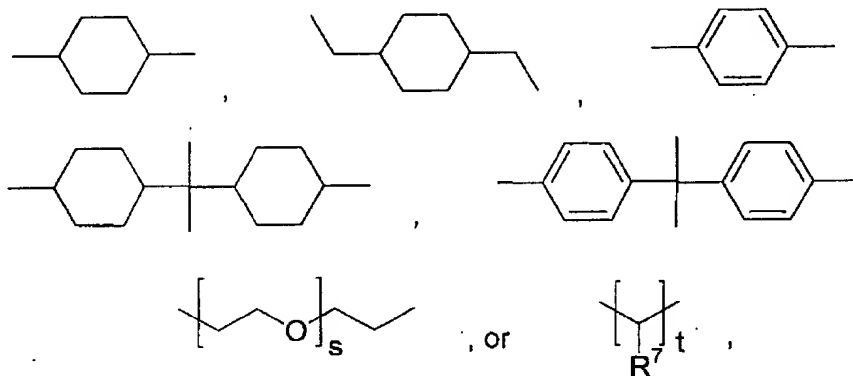
R\* is a C<sub>1-4</sub> alkyl;

n is an integer of at least 5; and

A is R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, or R<sup>4</sup>, whereR<sup>1</sup> is:

where:

p is an integer of 1 to 20;

R<sup>5</sup> is hydrogen or C<sub>1-4</sub> alkyl; andR<sup>6</sup> is:

where:

s is an integer of 0 to 30;

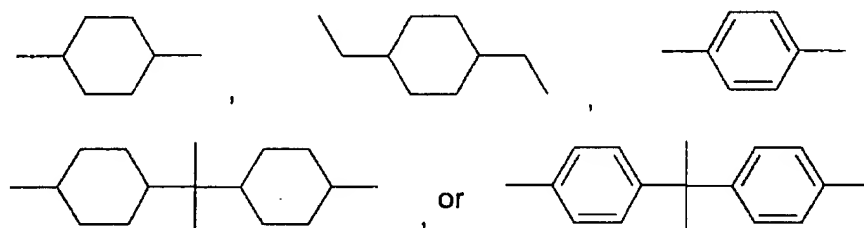
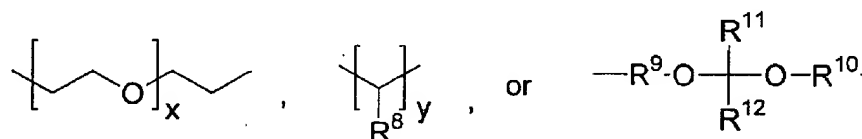
t is an integer of 2 to 200; and

R<sup>7</sup> is hydrogen or C<sub>1-4</sub> alkyl;



Application No. 09/854,435

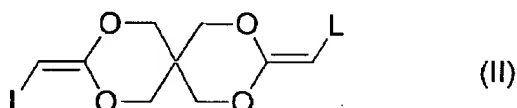
Page 15

 $R^2$  is: $R^3$  is:

where:

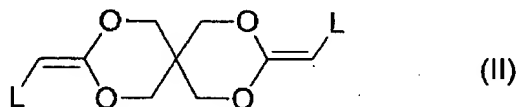
 $x$  is an integer of 0 to 30; $y$  is an integer of 2 to 200; $R^8$  is hydrogen or  $C_{1-4}$  alkyl; $R^9$  and  $R^{10}$  are independently  $C_{1-12}$  alkylene; $R^{11}$  is hydrogen or  $C_{1-6}$  alkyl and  $R^{12}$  is  $C_{1-6}$  alkyl; or  $R^{11}$  and  $R^{12}$  together are  $C_{3-10}$  alkylene; and $R^4$  is a diol containing at least one functional group independently selected from the group consisting of amide, imide, urea, and urethane groups;in which at least 0.1 mol% of the A units are  $R^1$ , and at least 0.1 mol% of the A units are  $R^4$ ,

the process comprising reacting a diketene acetal of formula II:

where  $L$  is hydrogen or a  $C_{1-3}$  alkyl,with a diol of the formula  $HO-R^1-OH$  and a diol of the formula  $HO-R^4-OH$ , and optionally at least one diol of the formulae  $HO-R^2-OH$  and  $HO-R^3-OH$ .

18. (Amended) A polyorthoester that is the product of a reaction between:

(a) a diketene acetal of formula II:

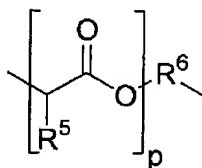
where  $L$  is hydrogen or a  $C_{1-3}$  alkyl, and

Application No. 09/854,435

Page 16

(b) a polyol or mixture of polyols in which at least 0.1 mole percent of the total polyol content is a diol of the formula  $\text{HO-R}^1\text{-OH}$ , where

$\text{R}^1$  is:

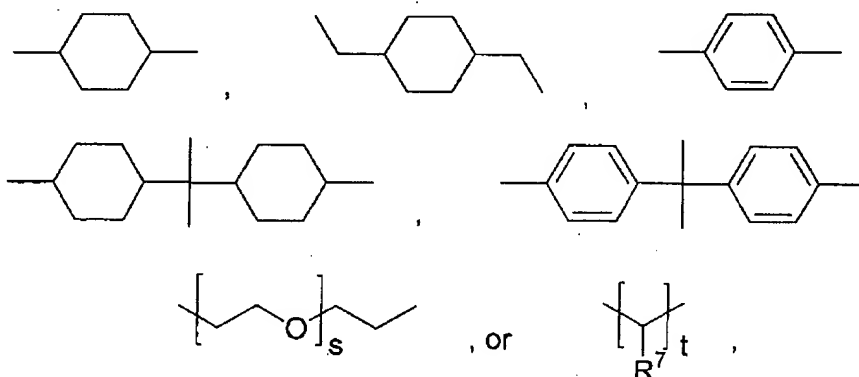


where:

$p$  is an integer of 1 to 20;

$\text{R}^5$  is hydrogen or  $\text{C}_{1-4}$  alkyl; and

$\text{R}^6$  is:



where:

$s$  is an integer of 0 to 30;

$t$  is an integer of 2 to 200; and

$\text{R}^7$  is hydrogen or  $\text{C}_{1-4}$  alkyl;

$\text{R}^{11}$  is hydrogen or  $\text{C}_{1-6}$  alkyl and  $\text{R}^{12}$  is  $\text{C}_{1-6}$  alkyl; or  $\text{R}^{11}$  and  $\text{R}^{12}$  together are  $\text{C}_{3-10}$  alkylene; and

at least 0.1 mole percent of the total polyol content is a diol of the formula  $\text{HO-R}^4\text{-OH}$ , where  $\text{R}^4$  is the residue of a diol containing at least one functional group independently selected from the group consisting of amide, imide, urea, and urethane groups.